Evaluation of the use of chimeric protein associated with Miltefosine as an immunochemotherapy strategy for the treatment of visceral leishmaniasis in the hamster Mesocricetus auratus.

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Visceral leishmaniasis (VL) is considered the most severe clinical form among leishmaniasis, with an incidence of approximately 16 million cases per year worldwide. Over the past 90 years, pentavalent antimony (Sb^{5+}) has been the recommended first-line drug for the treatment of VL. The high toxicity of this and other drugs, with reports of sudden death, is a limiting factor for their therapeutic use. In this sense, immunochemotherapy has been used as a promising strategy in the treatment of VL by associating drugs with immunomodulatory substances in order to achieve a therapeutic objective, with reduction of doses and toxicity. Thus, the objective of this study was to evaluate the therapeutic efficacy of the use of a chimeric protein (Chia A) associated/or not with Miltefosine and the adjuvant monophosphoryl lipid A (MPL) in a hamster model (Mesocricetus auratus). The animals were infected with $5x10^7$ promastigotes forms of Leishmania infantum (MCAN/ BR/2008/OP46) and were divided into three approaches. In the first approach, the animals received only chemotherapy with Miltefosine, 60 days post-infection and were divided into groups: (i) group treated for 14 days and (ii) group treated for 28 days. In the second and third approaches, the animals were subdivided into three groups: (i) group treated with MPL; (ii) group treated with Chi A + MPL and (iii) group treated with Miltefosine for 14 days + Chi A + MPL. In the second approach or serial form, the animals received treatment with immunotherapy serially, for 5 days with an interval of 10 days after the last dose, followed by treatment for another 5 days. In the third approach or isolated approach, the animals received treatment with immunotherapy in isolation, with two doses with an interval of 28 days. Infected and untreated animals were used as controls. The animals were evaluated in relation to the profile of cytokines produced by splenic cells (IFN-g and IL-10), through flow cytometry, 30 days after the end of each treatment. Preliminary results suggest that there was an increase in the production of IFN-g producing lymphocytes and a reduction of IL-10 producing lymphocytes per total lymphocytes, in the groups treated with Chi A in the absence or presence of miltefosine for 14 days both in the isolated approach. In the case of serial immunotherapy, treatment using Chi A promoted an increase in IFN-g producing lymphocytes. Furthermore, in this group, as well as in those associated with miltefosine, a reduction in the production of IL-10-producing lymphocytes was observed. Therefore,

our preliminary results demonstrate immunochemotherapy as a possible therapeutic potential against visceral leishmaniasis. In addition we highlight the imnovative potential of evaluations by flow cytometry in the hamster model.

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